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1 **Non-epithelial cancer dissemination: specificities and challenges**

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6

7 **Keywords**

8 Non-epithelial cancer, tumor dissemination, development, plasticity, tumor
9 microenvironment, therapy

10

11 **Abstract**

12 Epithelial cancers have served as a paradigm to study tumor dissemination but recent
13 data have highlighted significant differences with non-epithelial cancers. Here, we review
14 the current knowledge on non-epithelial tumor dissemination, drawing examples from the
15 latest developments in melanoma, glioma, and sarcoma research. We underscore the
16 importance of the reactivation of developmental processes during cancer progression and
17 describe the non-genetic mechanisms driving non-epithelial tumor spread. We also outline
18 therapeutic opportunities and ongoing clinical approaches to fight disseminating cancers.
19 Finally, we discuss remaining challenges and emerging questions in the field. Defining the
20 core principles underlying non-epithelial cancer dissemination may uncover actionable
21 vulnerabilities of metastatic tumors and help improve the prognosis of patients with
22 cancer.

23 **Main text**

24 **Introduction**

25 Our understanding of the metastatic process has improved significantly over the
26 past three decades [1]. Loss of cell-cell adhesion enables cells to detach from the primary
27 tumor and invade nearby tissues. Some of these cells enter the bloodstream or lymphatic
28 system via intravasation, facilitating their reaching distant sites where they may form
29 macro-metastases after exiting the vascular system by extravasation. These steps are
30 well-studied in epithelial cancers that arise from epithelial tissues like the lungs, colon, or
31 mammary gland. The epithelial to mesenchymal transition (EMT), a developmental
32 program involved in the migration and differentiation of cells from their original cell layers
33 and required for proper embryo patterning, is central to the dissemination of these tumors.
34 It encompasses remodeling cell interactions with the local environment, breaking the
35 basement membrane, and activating mesenchymal traits, thus boosting cell motility and
36 metastatic potential [2].

37 In non-epithelial tumors that arise from organs with intrinsically mesenchymal
38 features, the transitions between proliferative and invasive cell states that allow tumor
39 cells to undergo reversible non-genetic adaptation to their environment have been termed
40 “phenotype switching” [3]. In contrast to the extensive characterization of EMT, the
41 mechanisms underlying phenotypic plasticity in non-epithelial cancers during metastatic
42 colonization remain largely elusive and only partially align with the observations made in
43 epithelial cancers (Figure 1). In particular, the developmental origin of cancers determines
44 the range of accessible transcriptional states, such that cancers arising from mesodermal
45 or neural crest (NC)-derived cell types show higher mesenchymal scores and tend to

46 reside within a narrower portion of the EMT spectrum compared to tumors of epithelial
47 origins [4]. Accordingly, they exhibit higher invasive and metastatic potentials, mirroring
48 the behaviors of their developmental cell layer of origin. The epithelial or mesenchymal
49 nature of the cell of origin also impacts the role of cell adhesion and mode of migration in
50 metastatic progression. Because cell types originating from the NC do not naturally form
51 adherens junctions, alterations in cell-cell adhesion are less likely to be implicated in non-
52 epithelial cancer spreading. Similarly, non-epithelial tumors may prefer to migrate as
53 single cells, as collective migration relies on intact cell-cell junctions [5].

54 Epithelial and non-epithelial tumors also differ in their preferred routes of
55 metastasis (Figure 1). While epithelial tumors often spread through blood, some sarcomas
56 that originate from mesenchymal tissues like muscle or bone directly invade adjacent
57 tissues and other non-epithelial cancers like melanoma exhibit a propensity to lymphatic
58 metastasis. Brain tumors, such as glioblastoma, are a unique case, as local invasion
59 inside the brain is an already potentially lethal event, such that distant organ metastasis
60 is rarely observed. Metastatic tropism, defined as the preferential colonization of specific
61 target organs, is influenced by molecular compatibility between cancer cells and the target
62 organ as well as embryonic origins and varies widely between cancer types [6]. Non-
63 epithelial tumors display a broader range of metastatic sites compared to epithelial tumors
64 that are more influenced by vascular topology, according to Ewing's "mechanical
65 entrapment hypothesis" [6]. The concept of organotropism is reminiscent of the "seed and
66 soil" theory formulated by Paget in 1889, according to which metastatic sites are
67 determined by the affinity of neoplastic cells for the microenvironment of the host tissue.
68 However, it has since been proposed that if the "soil", the host tissue, presents

69 unfavorable microenvironmental conditions, cancer cells may enter a dormant state and
70 only emerge years after arriving at the distant site [7], suggesting that the “seed” and “soil”
71 are not fixed in time. Since awakening of dormant cancer cells relies on their capacity to
72 interpret signals from the surrounding host tissue, it is likely that epithelial and non-
73 epithelial cancers have different mechanisms of dormancy escape.

74 This review aims to highlight the specificities and gaps in knowledge of non-
75 epithelial tumor dissemination, drawing examples from recent findings on the cancers of
76 neuroectodermal and mesodermal origins melanoma, glioblastoma, and sarcoma. We will
77 first draw parallels between embryonic development and the origin of metastatic traits. We
78 will then present non-genetic mechanisms taking place during the metastatic cascade and
79 influencing the spreading ability of non-epithelial tumor cells. Since metastasis remains
80 responsible for most therapeutic failures and cancer-related deaths, we will also review
81 the arsenal of therapeutic strategies currently under development to specifically tackle
82 tumor dissemination. Finally, we will underscore pending questions that need addressing
83 in order to advance therapeutic approaches against aggressive cancers.

84

85 **The developmental origin of cancer spreading**

86 Epithelial cancers arise from epithelial tissues mainly of endodermal origin, while
87 non-epithelial cancers originate from mesenchymal or neural precursors of ectodermal or
88 mesodermal origin, both reflecting the characteristics of their embryonic progenitors.
89 Cancer progression often mirrors embryonic development. In carcinoma, EMT involves
90 transcription factors like SNAIL, TWIST1, SLUG, ZEB1, and ZEB2, known for driving both

91 morphological and molecular changes [2]. Yet, EMT was first observed in NC stem cells
92 during early development, as they migrate from the neural tube to various embryo
93 locations. NC-derived cells, including melanocytes, Schwann cells, and osteoblasts, can
94 give rise to melanoma, some brain tumors, and certain sarcomas, respectively (Figure 2).
95 Gene networks governing EMT in NC cells partially overlap with those in epithelial cancer
96 progression and are hijacked during metastatic spread by non-epithelial cancers [8].
97 Despite the unique tissue features of the central nervous system, transcription factors
98 (TFs) involved in EMT, such as ZEB1, can also induce mesenchymal traits in glioblastoma
99 [9]. Similarly, sarcoma cells may undergo processes reminiscent of partial EMT and
100 mesenchymal-to-epithelial transition (MET) during tumor progression and metastasis [10].

101 While both epithelial and non-epithelial cancers can co-opt EMT-like programs,
102 their metastatic phenotypes show distinct characteristics linked to their cell of origin. NC
103 development extends beyond EMT, involving traits like migration, resilience in challenging
104 environment, and distant colonization akin to metastasis. Melanoma progression hinges
105 on reacquiring a NC cell state marked by the re-expression of embryonic genes like
106 SOX10 and TFAP2 [11]. When transplanted into avian embryos, aggressive melanoma
107 cell lines mimic NC stem cell migration, unlike melanocytes and non-invasive melanoma
108 cells [12]. This behavior is also observed in other NC-derived tumors like neuroblastoma
109 (NB), whereas epithelial cancers like breast cancer do not follow NC embryonic migratory
110 paths. The underlying molecular signature is present in melanoma and
111 pheochromocytoma but absent in epithelial cancers [13]. This suggests shared cell states,
112 environmental responses, and transcriptional programs between malignant cells and
113 embryonic precursors in metastasis (Figure 3).

114 Reactivating developmental programs in transformed cells involves multiple
115 epigenetic factors, enhancing plasticity and enabling reversible transitions between
116 phenotypic states. For example, invasive melanoma cells can revert to an immature
117 melanoblast state with low MITF and high AXL expression by inducing dedifferentiation
118 through the expression of genes like SOX2, SOX9, and TGFB [14]. The molecular
119 pathways driving melanoblast migration during embryonic development appear crucial for
120 the motility of melanoma cells and ultimately metastasis. In mice, loss of P-Rex1, a Rac-
121 specific guanine nucleotide exchange factor, impairs melanoblast migration and prevents
122 melanoma metastasis [15]. Recent work identified additional melanoblast-specific genes
123 that contribute to melanoma metastatic ability in mouse, including KDELR3 that plays a
124 similar role in metastasis and development by promoting adaptation to ER stress [16].
125 Interestingly, these melanoblastic genes appeared co-regulated, suggesting the
126 reactivation of a whole epigenetic program.

127 Single-cell technologies have uncovered different cell states and their associated
128 transcriptional programs in tumors [17]. Among those identified in melanoma, the MITF^{low}
129 invasive phenotype encompassed two overlapping but distinct subpopulations:
130 dedifferentiated mesenchymal-like and NC stem cell-like [17-19]. The latter resembles NC
131 stem cells and expresses genes from the glial lineage, glioblastoma pro-neural genes,
132 and quiescent stem cell markers [18]. Interestingly, the dedifferentiated mesenchymal-like
133 state, characterized by PRRX1 expression, does not contribute to tumor expansion but
134 comprises metastasis-initiating cells adaptable to environmental challenges through cell
135 state transitions [17]. Single-cell analysis of human epidermal melanocytes across
136 different anatomical sites, developmental age, sexes, and skin tones, has revealed

137 dedifferentiation patterns that persist in melanoma and correlate with patient prognosis
138 [20]. Overall, these findings suggest that the aggressive nature of melanoma is rooted in
139 unique features of the melanocytic lineage.

140 The concept of glioblastoma "cancer stem cells" (CSCs) emerged a decade ago.
141 Recent research has unveiled a complex CSC hierarchy with a spectrum of stem-like cell
142 states influenced by genetics and the microenvironment [21]. Single-cell RNA sequencing
143 of 70,000 glioblastoma CSCs from 26 short-term cultured tumors identified a
144 transcriptional gradient from a highly proliferative "developmental state" activating a
145 neurodevelopmental program to an "injury response state" marked by mesenchymal-like
146 gene expression and a wound healing signature [22]. Importantly, self-renewal was
147 confined to the developmental state, but both states could form tumors in mice. Another
148 study including 36 glioblastoma patients classified cells by biological pathways,
149 highlighting the existence of neuronal / proliferative / progenitor and glycolytic /
150 plurimetabolic / mitochondrial axes [23]. However, these studies did not establish a clear
151 link between cell states and brain invasion. Recent in vivo imaging showed that
152 glioblastoma cells lacking contacts with other cancer cells and astrocytes expressed
153 neural genes and invaded the brain with neuron-like movements [24]. Activation of
154 glutamatergic neurogliomal synapses, observed during development of brain and spinal
155 cord neural networks, enhanced invasiveness through tumor microtubule formation (Figure
156 3).

157 Unlike melanoma and glioblastoma, our understanding of embryonic signaling and
158 oncogenic dedifferentiation in sarcomas remains limited. Ewing sarcoma cells, although
159 considered undifferentiated, have the potential to switch between epithelial and

160 mesenchymal-like states depending on the expression of the driving EWSR1-FLI1
161 oncoprotein [25]. Moreover, in some sarcomas, mesodermal patterning genes like
162 ALDH1A family members or the Wnt/B-catenin pathway, crucial during embryonic
163 development, regulate metastasis [26, 27] (Figure 3). Together, these findings suggest
164 that the invasive and metastatic abilities of non-epithelial cancer cells involve reactivating
165 developmental transcriptional programs and regaining immature cell states from cognate
166 embryonic lineages. Consequently, embryonic molecular signatures could complement
167 clinical parameters used to stratify patients according to their metastatic risk and may
168 conceal potential therapeutic targets in advanced tumors.

169

170 **Mechanisms of tumor dissemination in non-epithelial cancers**

171 Each metastatic cancer cell represents an evolutionary offshoot of the parental
172 primary tumor, sharing genetic mutations and acquiring the ability to spread. In pancreatic
173 cancer, early research found similar mutations in both primary tumors and metastases
174 [28] and recent genomic studies failed to identify distinct genetic factors of tumor
175 dissemination, suggesting the absence of a unique genetic signature of metastasis [29].
176 Similar observations were made in non-epithelial cancers [30]. Hence, metastatic potential
177 mainly arises from epigenetic changes and interactions between cancer cells and their
178 environment.

179 Epithelial cell changes, like E-cadherin loss in breast cancer, can promote
180 detachment and spreading from the primary tumor, although E-cadherin's role in
181 metastasis has recently been reevaluated [31]. During tumor progression, non-epithelial

182 cancer cells can switch between mesenchymal and amoeboid modes of migration or
183 between individual and collective spreading [32]. Amoeboid migration is characterized by
184 rounding of the cell body, increased plasma membrane flexibility, intense Rho/ROCK-
185 driven Myosin II activity, and limited cell-ECM interaction and matrix degradation [33]. In
186 contrast, mesenchymal migration involves strong cytoskeletal forces, focal adhesion to
187 the extracellular matrix (ECM) via integrins, and matrix breakdown, regulated by FAK and
188 SRC kinases. In the brain, the invasiveness of glioma stem cells depends on specific
189 adhesion molecules, including N-cadherin via ROBO1 regulation [34]. In metastatic
190 melanoma, loss of adherens junction protein NECTIN1 is frequent, but does not directly
191 cause melanoma spread [35]. Instead, it influences how tumor cells respond to
192 environmental stress. When IGF1 is scarce, melanoma cells establish adherens junctions
193 via NECTIN1, mimicking epithelial behavior and preventing dissemination. Without
194 NECTIN1, however, cancer cells shift to cell-matrix adhesion and migrate away. Adhesion
195 defects thus co-operate with microenvironmental changes to modulate melanoma cell
196 behavior.

197 To shift between different states and develop migratory abilities, cancer cells
198 undergo extensive transcriptional and epigenetic changes. This adaptability is most
199 pronounced in non-epithelial tumors and can be influenced by external factors like drug
200 treatment and hostile environments encountered during metastasis (Figure 4). Short-term
201 or moderate stress elicits transcriptional adaptation while prolonged or acute stress leads
202 to deeper changes driven by feedback loops and fixed by epigenetic mechanisms. EZH2,
203 a methyltransferase, is a key epigenetic regulator of melanoma metastasis that represses
204 tumor suppressor genes while also contributing indirectly to the upregulation of a set of

205 genes linked to motility in vivo [36, 37]. These genes are crucial for melanoma cells to
206 respond to pro-migratory signals within the primary tumor microenvironment (TME) and
207 to promote extravasation into the lung parenchyma. Similarly, PHF8, a histone
208 demethylase, modulates the TGFB pathway, promoting melanoma invasion [38]. In Ewing
209 sarcoma, the EWS-FLI1 fusion protein drives aberrant changes in chromatin structure and
210 transcription, fueling tumor heterogeneity [39]. In glioblastoma, specific transcriptional
211 programs correspond to different environmental niches, highlighting the reversible and
212 context-dependent nature of cell states within the TME. Cells in vascular regions exhibit
213 a 'pro-neural profile' driven by EZH2, while hypoxic areas display a BMI1-dependent
214 mesenchymal signature [40].

215 Interactions between cancer cells and their environment within primary tumors and
216 during spreading play a crucial role in metastasis (Figure 4). In melanoma, a crosstalk
217 between tumor and TME cells leads to the upregulation of a common cilia gene signature
218 controlled by ETS-family transcription factors specifically at the invasive front [41].
219 Invasion through the dermis brings melanoma cells in contact with adipocytes, from which
220 they acquire lipids via FATP/SLC27A lipid transporters, thus bypassing the need for de
221 novo lipogenesis to fuel their spread [42]. Dermal fibroblasts also promote melanoma
222 metastasis through increased secretion of sFRP2 and angiogenesis [43]. Similarly,
223 glioblastoma spreading relies on interactions with astrocytes mediated by gap junction
224 proteins, such as Connexin-43, which activate the NF- κ B pathway that plays a key role in
225 invasion [44].

226 Remodeling of the microenvironment during metastasis includes alterations in
227 tumor immunity establishing an environment conducive to immune evasion. In

228 glioblastoma, single-cell studies revealed an immunosuppressive niche associated with
229 hypoxia and developmental gene expression triggering macrophage polarization, T-cell
230 suppression, and cancer cell migration via macrophage CCL2 release [45]. Astrocytes
231 promote melanoma brain metastasis by stimulating LCN2 and pro-inflammatory
232 pathways, attracting immunosuppressive myeloid cells [46]. In sarcoma, complement
233 effectors C3 and C3aR create an immunosuppressive environment by altering tumor-
234 associated macrophages and inhibiting T-cell activation [47]. Immune cells can also shape
235 tumor cell states in return. In glioblastoma, macrophages release oncostatin, activating
236 STAT3 and promoting a mesenchymal-like state associated with reduced MHC-I and
237 MHC-II expression and T cell skewing away from cytotoxic states [48]. Furthermore, the
238 acquisition of mesenchymal features by cancer cells enhances their ability to evade the
239 immune system, as illustrated in melanoma where immune escape and resistance to
240 immunotherapies have been linked to a dedifferentiated, invasive cell state and to the
241 upregulation of adhesion pathways, angiogenesis and ECM remodeling [49]. Similarly,
242 activation of migratory mechanisms driven by the ROCK-Myosin II pathway stimulate the
243 production of an immunomodulatory secretome inducing tumor-promoting macrophage
244 differentiation and angiogenesis [50].

245 Disseminating tumor cells adapt their metabolism to changing environments
246 depending on progression stage and location. Brain metastases in melanoma were
247 categorized as "immune-enriched" or "immune-deficient" through RNA sequencing, with
248 the latter linked to worse patient survival and increased oxidative phosphorylation [51].
249 This metabolic shift appears unique to brain metastasis and influences dissemination.
250 Moreover, melanoma cells modify fatty acid metabolism to resist oxidative stress in lymph

251 and blood, relying on NADPH-generating enzymes and overexpression of
252 Monocarboxylate Transporter 1 (MCT1) [52, 53]. Lineage-specific programs play a role in
253 metabolic rewiring, suggesting that they might differ between epithelial and non-epithelial
254 tumors. For instance, low MITF expression constrains the expression of the long chain
255 fatty acid desaturase SCD, promoting a dedifferentiated and invasive state in melanoma
256 [54]. Cellular adaptation to external cues, transcriptomic and epigenetic plasticity,
257 remodeling of the microenvironment, and metabolic reprogramming all contribute to the
258 remarkable capacity of non-epithelial cancers to spread.

259

260 **Targeting vulnerabilities of metastatic cancer cells**

261 Despite significant progress in cancer drug development, survival rates of patients
262 with metastatic disease remain low. The development of treatments focused on the
263 properties of disseminated tumor cells is direly needed [55]. The initial strategy against
264 metastasis was the development of 'migrastatics', drugs impeding cancer migration and
265 invasion, especially promising against non-epithelial tumors displaying mesenchymal
266 traits and high migratory propensity [56]. Recently, ROCK inhibitors emerged as
267 neoadjuvant therapy options in melanoma, where ROCK signaling associates with a
268 dedifferentiated cell state and immune evasion [57]. ROCK inhibitors specifically kill drug-
269 resistant cells through reactive oxygen species and unresolved DNA damage and improve
270 immune responses. Moreover, melanoma cells with high RhoA/ROCK signaling are
271 capable to survive in the bloodstream by relying on actomyosin contractility, suggesting
272 that ROCK inhibitors could reduce the risk of dissemination [58] (Figure 5).

273 Understanding plasticity mechanisms has pointed to epigenome targeting as a way
274 to alter cancer cell dedifferentiation during metastasis [59]. HDAC inhibitors have shown
275 promise in pre-clinical studies in sarcoma by inhibiting several pathways, including those
276 involved in metastasis [60]. Furthermore, EZH2 activity upholds an undifferentiated state
277 in Ewing sarcoma [61] and is an essential driver of melanoma metastasis [36],
278 representing a potential therapeutic target. “Directed phenotype switching” represents
279 another strategy to exploit cancer plasticity therapeutically. It aims to force
280 undifferentiated, migratory cell states into a more differentiated, proliferative state
281 targetable by conventional chemotherapies. In melanoma, the migratory MITF^{low} cell
282 populations depend on RXRG, a vulnerability that can be therapeutically exploited by pan-
283 RXR antagonists [18]. Moreover, specific features of this state, like the upregulation of the
284 AXL receptor, can be effectively leveraged by anti-AXL antibody-drug conjugates for
285 precise delivery of a microtubule-disrupting agent [62]. In glioblastoma, the use of a
286 DYRK1A/B inhibitor to target a slow-cycling infiltrating subpopulation expressing the stem
287 cell marker Prominin-1, reduces brain invasion [63] (Figure 5).

288 Yet, therapeutic targeting of metastasis should not only address the plasticity of
289 cancer cells but also mechanisms used by dormant cells to awaken and evade tumor
290 surveillance. Immunotherapy offers promise to eradicate or control metastatic disease, as
291 microenvironmental cues influencing dormancy include neutrophil and myeloid
292 compartments [64]. While in melanoma, immunotherapies have already made durable
293 remissions possible for patients with stage IV disease [65], in sarcoma, metastatic sites
294 show higher T lymphocyte infiltration compared to primary tumors, suggesting a potential
295 for T-cell targeted therapy in advanced-stage disease [66]. Other therapies targeting TME

296 components are currently under investigation. Emerging strategies involve depleting
297 cancer-promoting cells or reprogramming them toward immune-stimulating or tumor
298 suppressive phenotypes [67]. For example, neutralizing antibodies and small molecule
299 inhibitors have effectively eliminated tumor-associated macrophages or promoted their
300 switch to an anti-tumor phenotype in preclinical models of various solid tumors, including
301 glioblastoma [68] (Figure 5).

302 Recent findings link drug resistance and tumor spread, suggesting shared nodes
303 that could enhance anti-cancer therapies [69]. Adhesion pathways crucial for cell survival
304 largely overlap with invasion-promoting signaling, such as FAK-SRC, RhoA-ROCK, and
305 PI3K/AKT pathways [57, 70]. In melanoma, migration-inducing RTKs like AXL confer
306 resistance through MAPK/JNK pathway by interacting with tumor-associated
307 macrophages [71]. HDACs also bridge metastasis and therapy resistance by controlling
308 survival and invasion programs via AKT and MAPK signaling, as shown in glioblastoma
309 [70]. Mechanochemical stress sensed by the Hippo pathway during cancer migration can
310 also boost therapy resistance in sarcoma [72], while in melanoma, YAP, the key Hippo
311 pathway effector, promotes the acquisition of an invasive signature and fosters
312 spontaneous metastasis [73]. Overall, identifying shared pathways between metastasis
313 and resistance could suggest new strategies to abrogate both survival and dissemination.
314 Developing a dedicated therapeutic arsenal for metastasis may open a new era of
315 combination treatments for lasting tumor control in metastatic cancer patients.

316

317 **Emerging concepts in non-epithelial cancer dissemination**

318 A “late dissemination” model postulates that only the fittest primary tumor cells give
319 rise to metastases, whereas an “early dissemination” model proposes that cells spread at
320 early, even possibly pre-neoplastic, stages of cancer development [74]. Circulating tumor
321 cells (CTCs), released from tumors into the bloodstream, offer a unique window on
322 metastasis although their success rate at colonizing distant organs is low (1-4%) [75].
323 Glioblastoma CTCs appear heterogeneous, exhibiting either stem cell or mesenchymal
324 traits [76], while in Ewing sarcoma, CTC detection at diagnosis predicts poor outcomes
325 and recurrent disease, underscoring their potential prognostic value [77]. Developing
326 devices to detect CTCs in large blood volumes and monitor their temporal release is
327 crucial for future research and clinical diagnostics (see Outstanding Questions).

328 The factors determining organotropism in cancer remain unclear. Lymph node
329 colonization has recently emerged as a prominent route for melanoma metastasis that
330 involves acquiring resistance to ferroptosis through increased membrane integration of
331 oleic acid [52]. Although genomic evidence suggests parallel, rather than consecutive,
332 colonization of lymph nodes and distant tissues by melanoma cells [74], lymph node
333 colonization may promote immune tolerance, thus facilitating distant tissue colonization
334 [78]. A recent study provided new insights into the patterns of melanoma metastatic
335 dissemination through extensive intra-patient analysis [79]. Notably, late-emerging brain
336 metastases displayed lower genome instability and earlier clonal phylogeny divergence
337 than other sites, supporting the idea that melanoma cells may disseminate early from the
338 primary tumor to both regional and distant sites. Brain metastasis is a significant cause of
339 mortality for patients with melanoma. A multi-omics single-cell atlas recently pointed to
340 neuronal differentiation signatures, variable metabolic pathways and limited type-I

341 interferon responses, as specific features of brain metastases that could be
342 therapeutically exploited [80].

343 In both epithelial and non-epithelial cancers, the establishment of pre-metastatic
344 niches (PMNs) supports disseminated cell survival and growth at distant sites, with recent
345 findings highlighting the role of tumor-secreted extracellular vesicles (EVs) – membrane-
346 bound structures released by cells into the extracellular space – in promoting these PMNs.
347 In melanoma, EVs can trigger myeloid cell recruitment to the lungs by downregulating
348 interferon signaling [81], while in osteosarcoma, EVs drive lung resident cells to favor
349 fibroblast conversion into tumor-promoting myofibroblasts, thus contributing to PMN
350 formation [82].

351 A key question in metastasis research is how fully transformed cancer cells may
352 not reinitiate growth at secondary sites for years or even decades. Recent studies reveal
353 that cancer cells in a foreign environment can enter a reversible dormant state, balancing
354 proliferation and death to persist in distant organs [7]. The cues regulating tumor cell
355 dormancy and reawakening are still being investigated but components of the TME seem
356 implicated. For instance, the secretion of sFRP1, a non-canonical WNT5A antagonist, by
357 lung fibroblasts of aged mice reactivates melanoma cell proliferation through the AXL-
358 MER axis downstream of WNT5A [83]. Strikingly, in human, organ transplants from donors
359 apparently disease-free but previously diagnosed with melanoma or glioblastoma have
360 led to tumor transfer to immunosuppressed recipients [84], suggesting that the immune
361 system maintains dormancy. However, the mechanisms by which dormant cells evade
362 immune cell killing remain unclear.

363

364 **Concluding remarks**

365 Examining the characteristics and mechanisms of metastasis in non-epithelial
366 cancers has revealed specificities in their dissemination modes, cell states reminiscent of
367 developmental programs, interactions with the tumor microenvironment, and molecular
368 adaptation to stress and therapy, providing a nuanced understanding of the complexities
369 involved in the spread of these aggressive cancers. CTC biology and the mechanisms of
370 dormancy and organotropism hold promise for new diagnostic tools and therapies for
371 metastatic cancers. Yet, how they differ between epithelial and non-epithelial tumors
372 remains an open question. Whether CTCs can represent tumor heterogeneity, predict
373 progression, and guide treatment is still unclear. In vivo models using barcoding for clone
374 tracking and molecular analysis are needed. Detecting dormant cells over time would also
375 enhance our understanding of metastatic progression. Moreover, advanced imaging,
376 spatial technologies, and computational approaches may provide a deeper resolution of
377 the metastatic niche. The generation of pre-clinical models mirroring human immunity to
378 study immune control of metastatic growth would represent another milestone on the road
379 to a complete characterization of the factors influencing metastatic colonization. There is
380 hope that these studies will lay the foundations for innovative therapeutic approaches
381 against advanced tumors.

382

383

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389

390

391 **Declaration of interests**

392 The authors declare no competing interests.

393

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576

577 **Highlights**

- 578 • Non-epithelial cancers exhibit specificities in their modes of dissemination, including
579 unique cell states, adhesion pathways, and routes of metastasis.
- 580 • Recent evidence indicate that progression of non-epithelial tumors involves
581 reacquisition of early developmental cell states of their lineage of origin.
- 582 • Interactions with the tumor microenvironment, including immune and stromal cells,
583 profoundly impacts cancer cell spread and response to treatment.
- 584 • Transcriptional and metabolic rewiring enables cancer cells to adapt to challenging
585 microenvironments encountered during metastasis.
- 586 • Tumor dissemination and drug resistance share molecular features that could be
587 exploited to fight aggressive cancers.

588

589 **Outstanding Questions**

- 590 • To what extent do epithelial and non-epithelial tumors differ in their organotropism,
591 quantity and timing of tumor cell shedding into circulation, and role of the tumor
592 microenvironment during spreading?
- 593 • What are the cellular and molecular bases of organotropism?
- 594 • What is the exact contribution of the microenvironment to tumor spreading, in both
595 primary tumors and metastatic niches?
- 596 • How can research on circulating tumor cells be effectively translated into clinical
597 practice?

- 598 • How can we therapeutically target cell states and microenvironmental cues
599 associated with tumor progression?

600

601 **Figure Legends**

602 **Figure 1 – Specificities and open questions in non-epithelial cancer dissemination.**

603 Metastasis unfolds through a series of orchestrated steps. 1) Invasion: cancer cells at the
604 primary tumor site acquire the ability to invade adjacent tissues through changes in cell
605 adhesion that are different between epithelial and non-epithelial tumors, and through
606 mechanisms that share some, but not all, features with epithelial-to-mesenchymal
607 transition (EMT). 2) Intravasation: invasive cancer cells breach into blood vessels or
608 lymphatic channels, depending on the tumor type, by interacting with endothelial cells,
609 disrupting endothelial junctions, and navigating through the endothelial cell layer. 3)
610 Survival in circulation: as cancer cells travel through the bloodstream or lymphatic system,
611 they encounter challenges such as shear forces and immune surveillance that they need
612 to withstand through specific adaptive mechanisms to survive. 4) Extravasation: cancer
613 cells arrest and exit the bloodstream or lymphatic vessels, often through interactions with
614 endothelial cells and a cell-state transition that may be different between epithelial and
615 non-epithelial tumors. 5) Colonization: having extravasated, cancer cells establish
616 themselves at the secondary site, forming micrometastases and/or entering dormancy.
617 Interactions with the local microenvironment govern the survival, awakening, and
618 proliferation of metastatic cells to form macrometastases. Steps of the metastasis

619 cascade that are, or may be, different between epithelial and non-epithelial tumors are
620 highlighted in red or green, respectively.

621

622 **Figure 2 – Developmental origin of non-epithelial cancers.** The neural crest, an
623 embryonic cell layer delaminating from the neural tube and exclusive to vertebrates, gives
624 rise to a diverse array of ectodermal derivatives, including melanocytes, Schwann cells,
625 and peripheral nervous system (PNS) neurons. Additionally, neural crest cells generate
626 chondrocytes and osteoblasts forming the facial skeleton, as well as a subset of smooth
627 muscle cells and adipocytes. In embryonic development, neuroectodermal cells from the
628 neural tube wall generate intermediate progenitor cells known as radial glial cells, which
629 subsequently differentiate into central nervous system (CNS) neurons and various glial
630 cells, such as astrocytes and oligodendrocytes.

631

632 **Figure 3 – Co-option of developmental pathways in cancer spreading.** Molecular
633 pathways regulating cell functions of neural crest cells, neural stem cells, and
634 mesenchymal stem cells during development have also been implicated in the growth and
635 migration of their corresponding tumors.

636

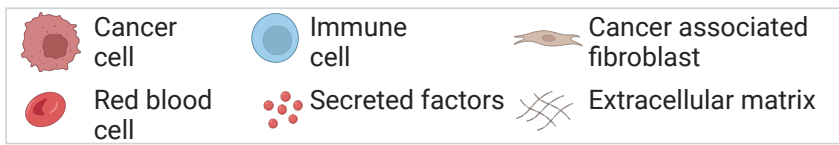
637 **Figure 4 – Non-genetic events in non-epithelial cancer dissemination.** Cells from the
638 tumor microenvironment through direct or indirect interactions, secreted factors, the
639 extracellular matrix, local chemical conditions and physical constraints, modulate the

640 transcriptional state of non-epithelial cancer cells through epigenetic rewiring, and
641 consequently influence their ability to spread.

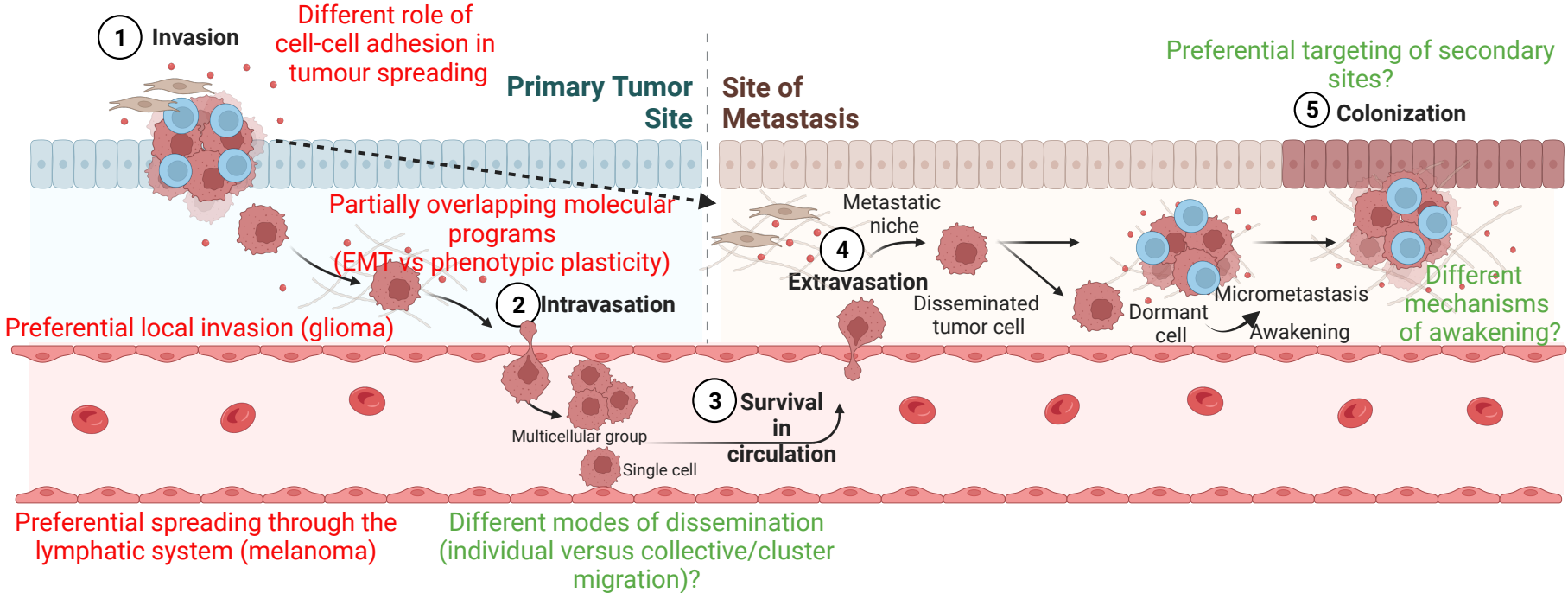
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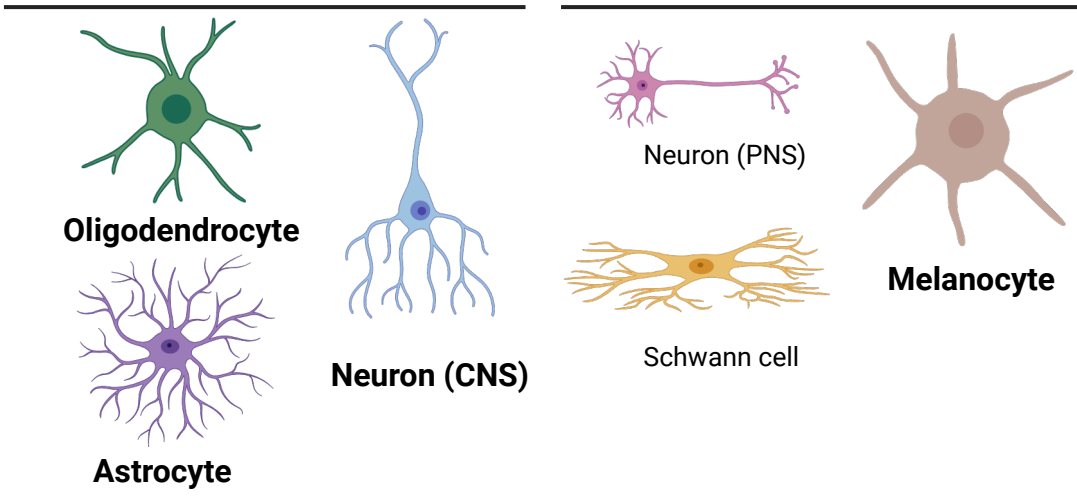
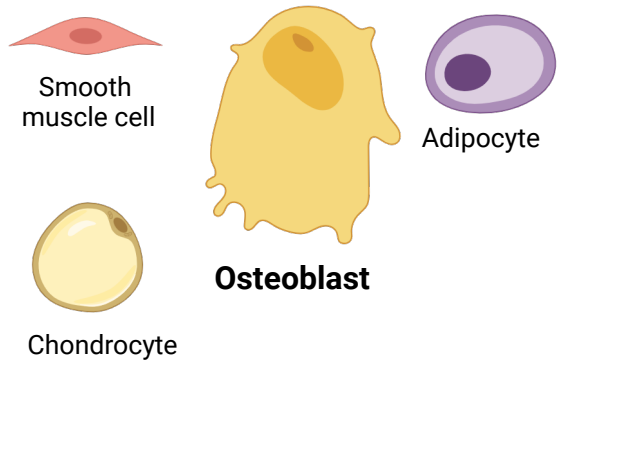
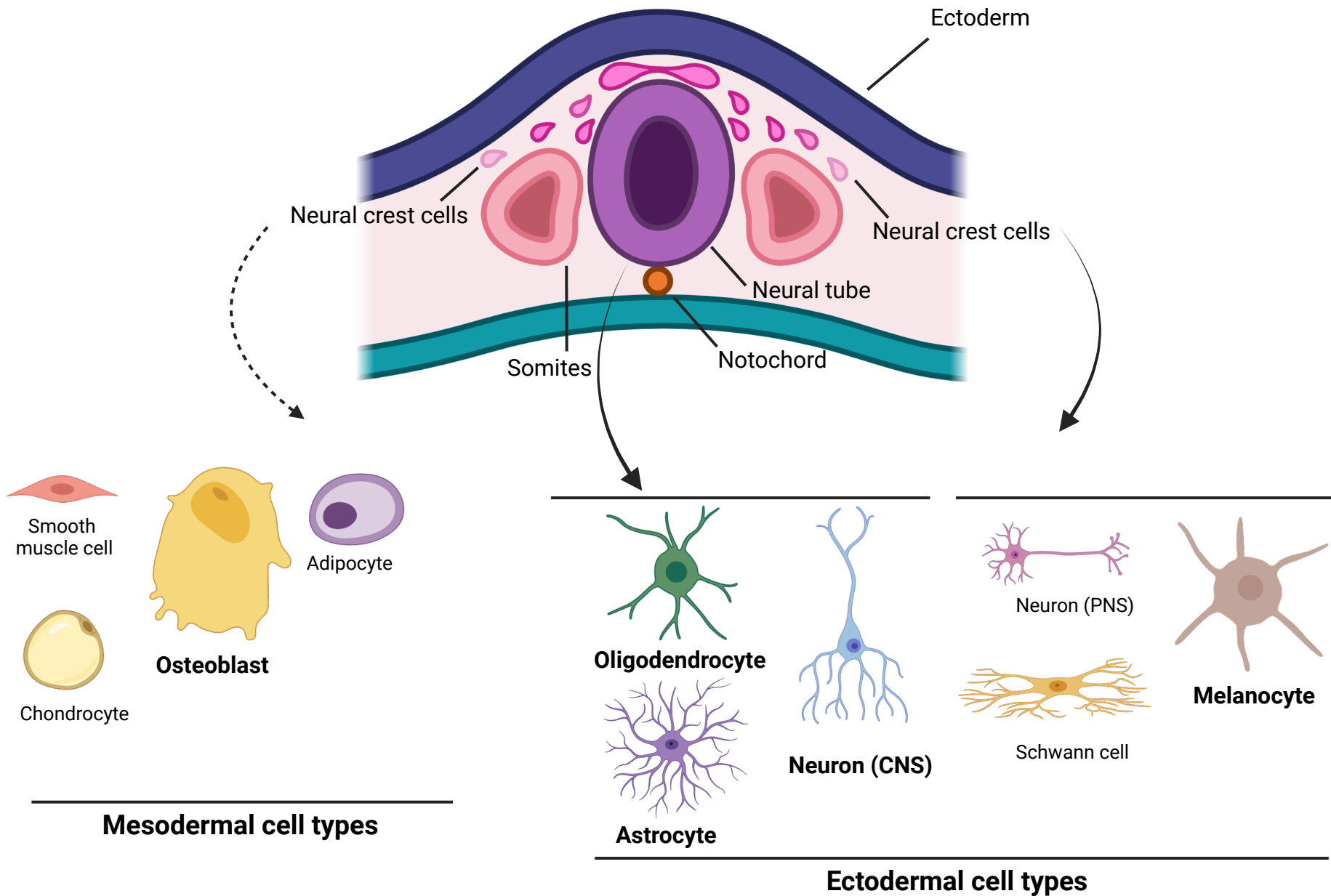
643 **Figure 5 – Targeting vulnerabilities of metastatic cancer cells.** Therapeutic
644 approaches against non-epithelial metastatic tumors include targeting invasion and
645 migration pathways, cancer cell plasticity, or the metastatic microenvironment by blocking
646 the molecular and cellular mechanisms involved in dissemination, adaptation to stress,
647 and survival at distant sites.

648



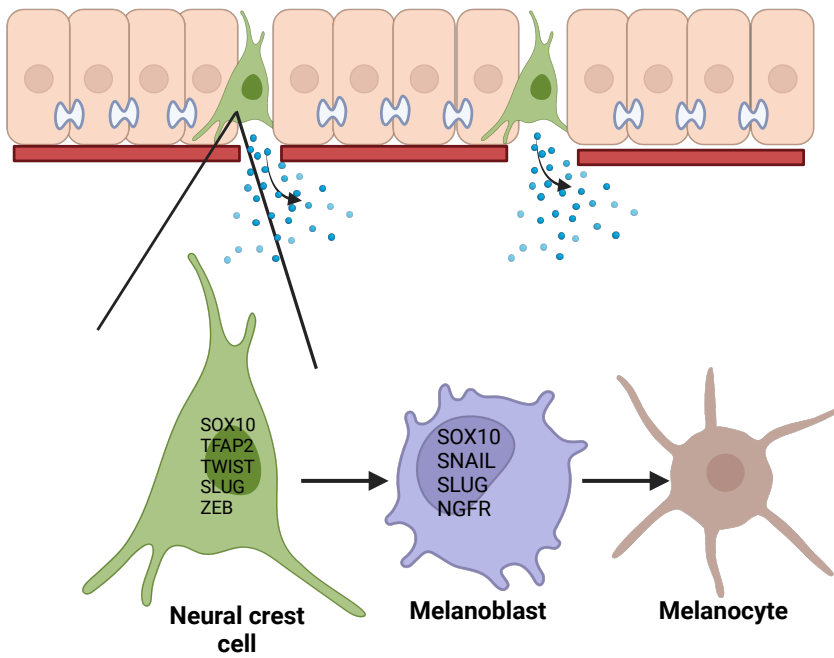
Different tissue of origin





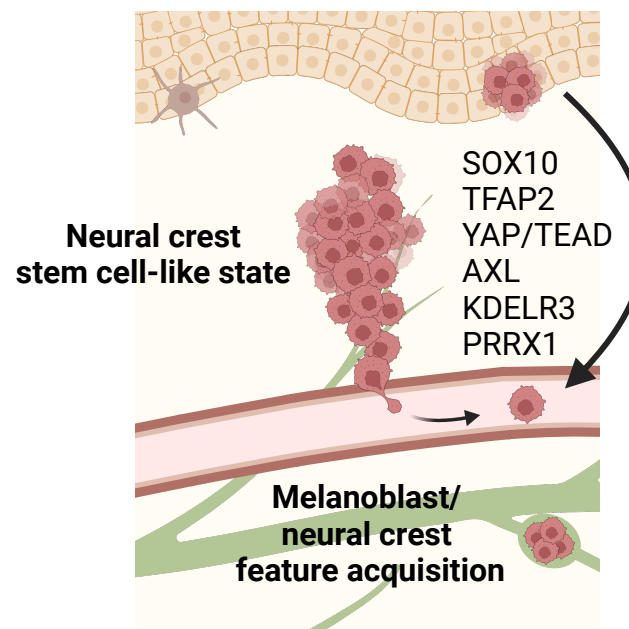
Development

Melanocyte

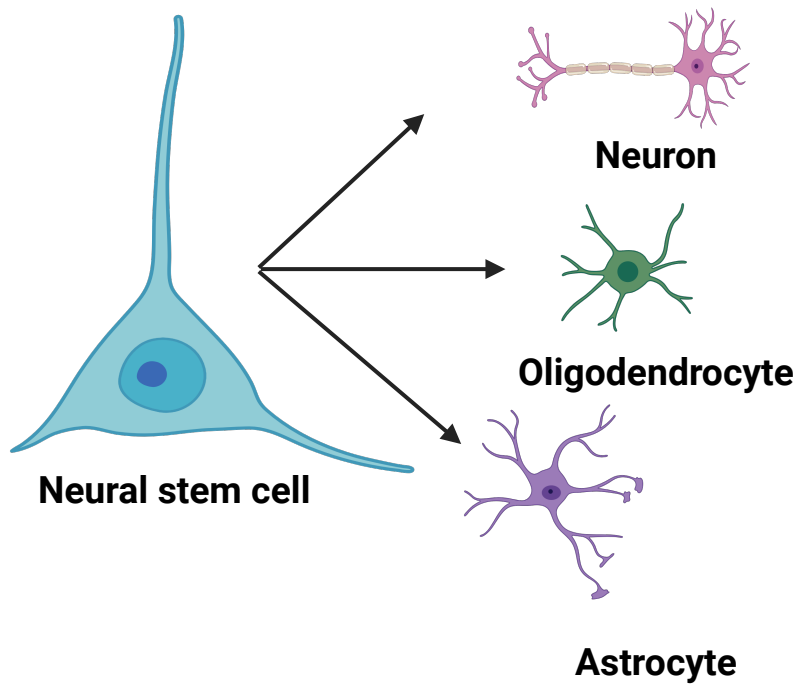


Metastasis

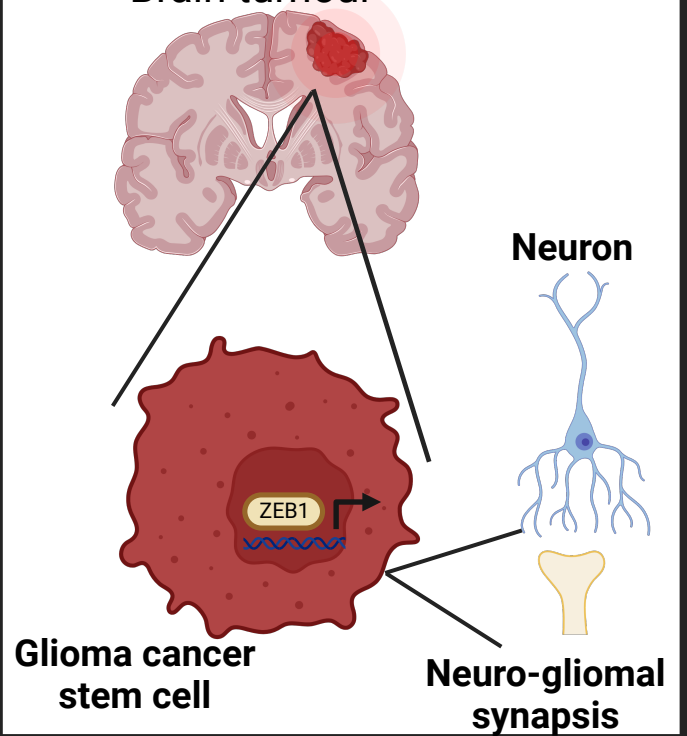
Melanoma



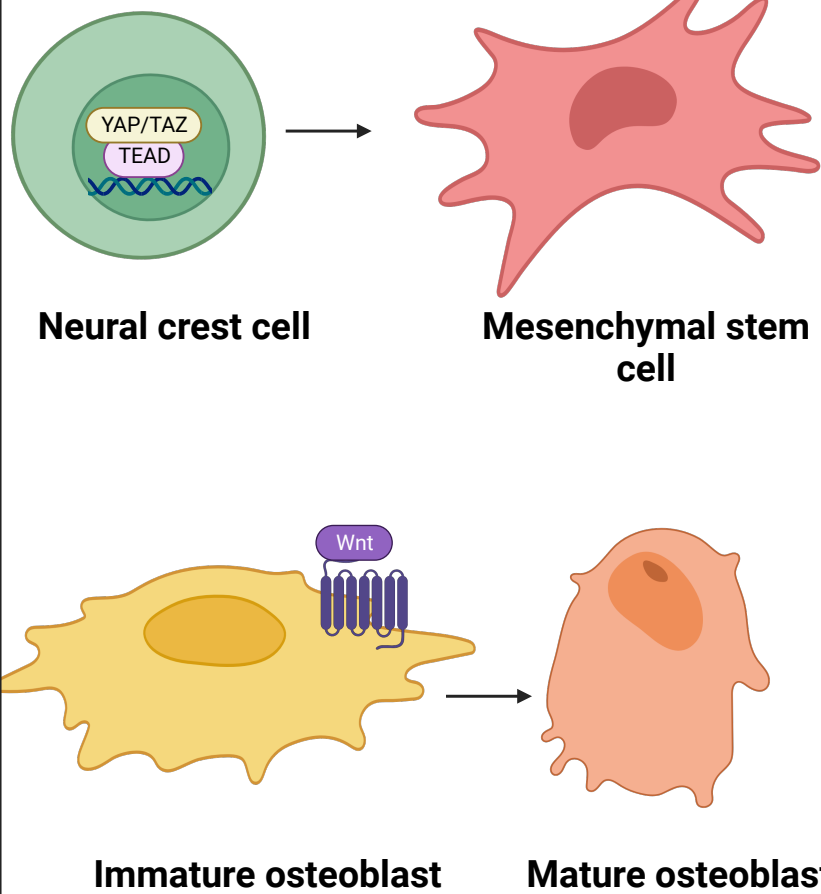
Neural cell



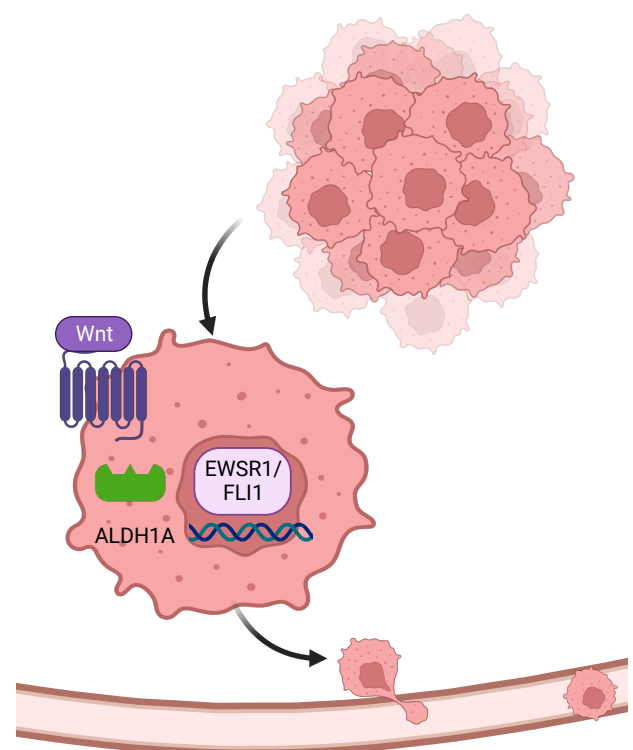
Brain tumour

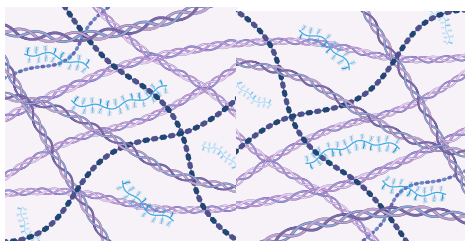


Osteoblast



Sarcoma

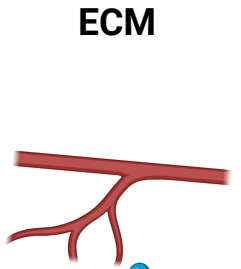




Local chemical conditions
(eg. hypoxia, oxidative stress)

Local physical constraints

ECM

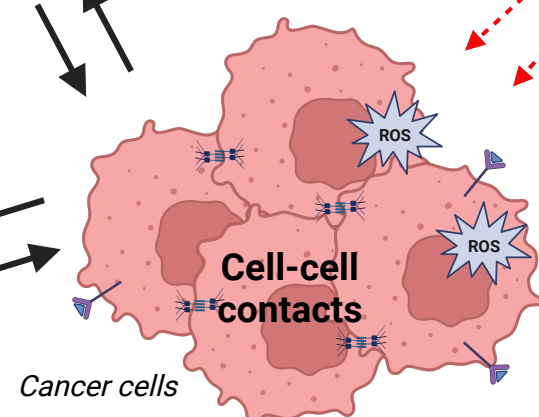


Secreted factors



Cancer associated fibroblasts

Endothelial cells

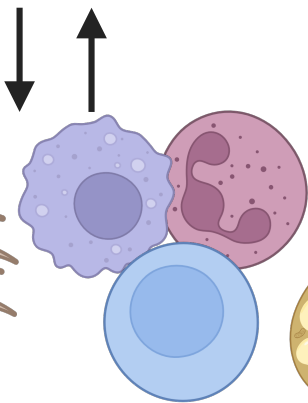


Cell-cell contacts

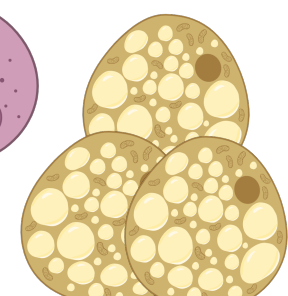
Cancer cells

ROS

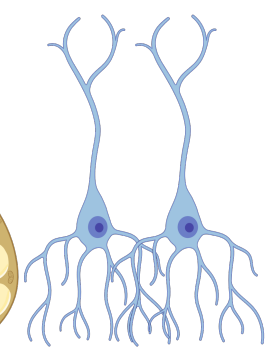
ROS



Immune microenvironment



Adipocytes



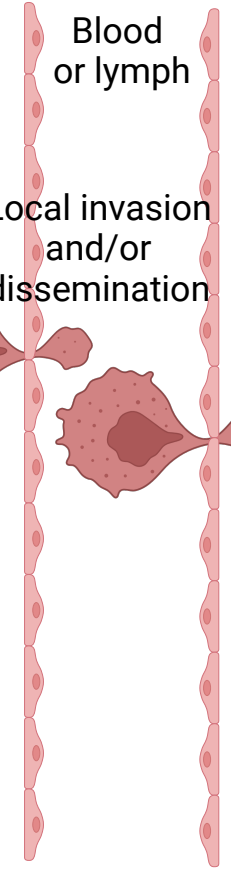
Neural cells

Transcriptional regulation



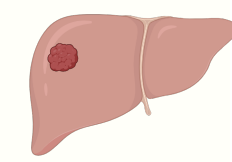
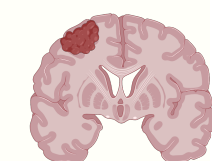
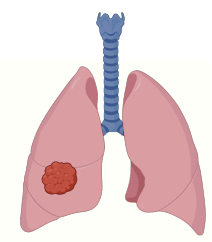
Metastatic cancer cell

Local invasion and/or dissemination



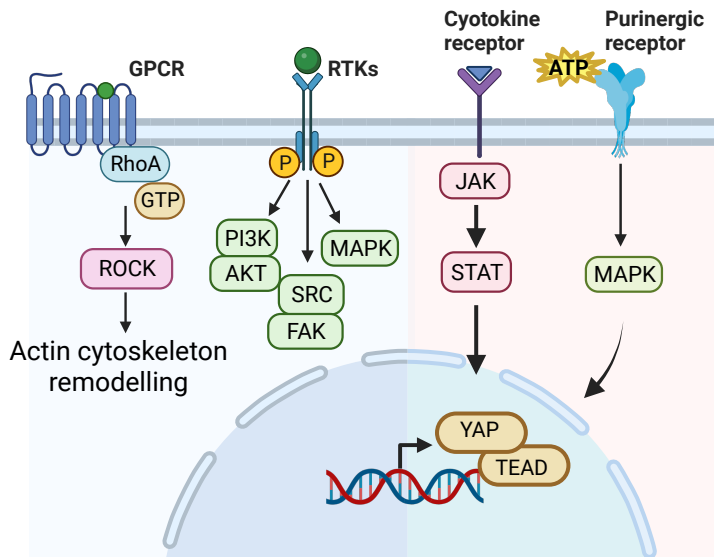
Blood or lymph

Secondary sites

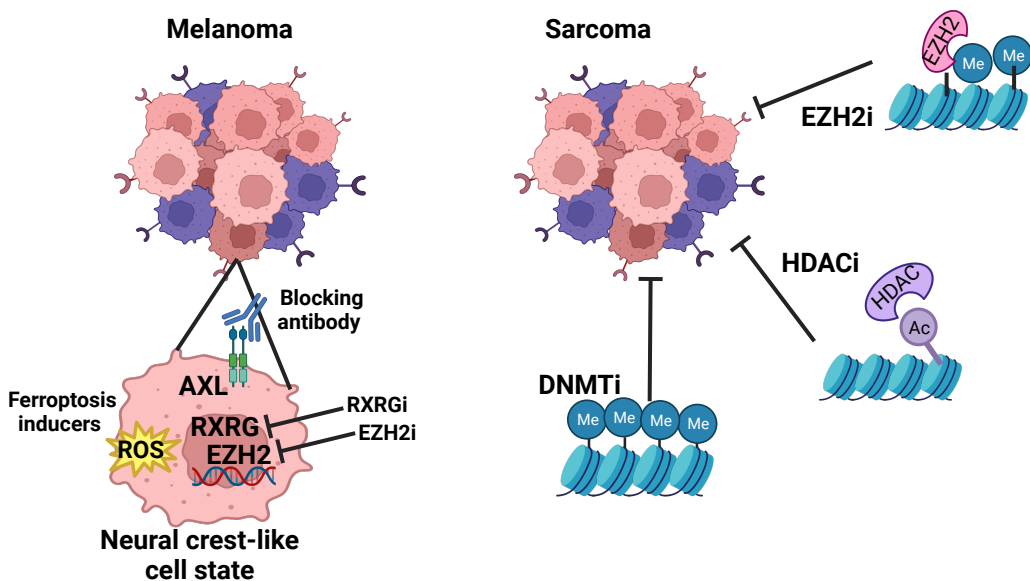


Tumor microenvironment cell types

Targeting invasion and migration pathways



Targeting cancer cell plasticity



Targeting the metastatic microenvironment

